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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/976,900	10/12/2001	Chad A. Mirkin	00-713-i23	3590

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EXAMINER
RILEY, JEZIA

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 05/14/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/976,900	MIRKIN ET AL.	
	Examiner	Art Unit	
	Jezia Riley	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *407-420 and 423-444* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *407-420,423 and 424* is/are rejected.

7)☒ Claim(s) *433-444* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 415 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

2. Claim 415 recites the limitation "the nanoparticle of the aggregate probe" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 407-420 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yguerabide et al. (6,214,560) in view of Sosnowski et al. (6,518,022).

Yguerabide et al. discloses a method of light illumination and detection named "DLASLPD" (direct light angled for scattered light only from particle detected) disclose an analyte assay using gold particulate label for specific detection of one or more analytes in a sample. One or more analytes in a sample can be detected and measured by detection and/or measurement of one or more of the specific light scattering properties of metal-like particles. (Summary of the Invention). For example, a certain nucleic acid analyte is composed of about 100 nucleic acid bases and is present in a sample. The sample is prepared so that this nucleic acid is in a single stranded form. Then two or more unique single-stranded "probe" nucleic acid sequences are added to the sample where these different probes bind to different regions of the target strand. Each of these probes has attached to one or more particles (col. 74). Further, the particles can form different types of aggregates that can be detected visually or instrumentally in a microscope or through macroscopic observation or measurements without having to separate free from analyte bound particles. The method provides for useful apparatus and particle types for specific test kits can be constructed. These different test kits, and associated apparatus are useful for applications to consumer use, portable field use, point of care applications such as

doctor's offices, clinics, emergency rooms and the like, research laboratories, and centralized high throughput testing.

Sosnowski et al. discloses a microelectronic based nucleic acid array which utilizes electric fields as an independent parameter to control transport, hybridization and stringency of nucleic acid interactions. These are "active" array devices in that they exploit microelectronic as well as microfabrication technology. Now, in addition to salt, pH, temperature and chaotropic agents, the electric field strength (in particular the current level and density) provides a precisely controllable and continuously variable parameter for adjustment of nucleic acid interactions. The invention features methods for detecting and analyzing reactions that have occurred at the addressed microlocations using self-addressed microelectronic devices with associated optical, optoelectronic or electronic detection systems or self-addressed microelectronic devices with integrated optical, optoelectronic or electronic detection systems which is viewed to be inclusive of a flatbed scanner.

One key aspect of this invention is played by the ion-permeable "permeation" layer which overlies the electrode. This permeation layer allows attachment of nucleic acids to permit immobilization. More importantly, the permeation layer separates the attached or tethered oligonucleotides and hybridized target DNA sequences from the highly reactive electrochemical environment generated immediately at the electrode surface. This highly reactive electrode surface and its electrochemical products can

rapidly destroy DNA probes and target DNA sequences which contact it or approach it too closely. This permeation layer thereby allows oligonucleotides and DNA fragments to be "electronically targeted" above the actual electrode surface and hybridized to anchored complementary oligonucleotides while being protected from the reactive surface and environment. Most importantly, the design of the microelectrode and permeation layer to form a microlocation structure, allows high current densities to be achieved in an extremely confined area, while minimizing the adverse effects produced by the electrode itself. One aspect of the invention is a device with an array of electronically programmable and self-addressable microscopic locations. Each microscopic location contains an underlying working direct current (DC) or DC/AC microelectrode supported by a substrate. The surface of each microlocation has a permeation layer for the free transport of small counter-ions, and an attachment layer for the covalent coupling of specific binding entities. These unique design features provide the following critical properties for the device: (1) allow a controllable functioning DC electrode to be maintained beneath the microlocation; (2) allow electrophoretic transport to be maintained; and (3) separate the affinity or binding reactions from the electrochemical and the adverse electrolysis reactions occurring at the electrode (metal) interfaces. The primary function of the micro-electrodes used in these devices is to provide electrophoretic propulsion of binding and reactant entities to specific locations.

Another aspect features a method for improving efficiency and stringency of nucleic acid hybridization reactions, comprising the steps of: rapidly concentrating dilute target DNA and/or probe DNA sequences at specific microlocation(s) where

hybridization is to occur; rapidly removing non-specifically bound target DNA sequences from specific microlocation(s) where hybridization has occurred; rapidly removing competing complementary target DNA sequences from specific microlocation(s) where hybridization has occurred; adjusting electronic stringency control (ESC) via current level and density to remove partially hybridized DNA sequences (more than one base mis-match); adjusting ESC via current level and density to improve the resolution of single mis-match hybridizations using probes in the 8-mer to 21-mer range(e.g., to identify point mutations); using ESC via current level and density, to utilize oligonucleotide point mutation probes outside of the ranges used in conventional procedures (e.g., probes longer than 21-mers and shorter than 8-mers); for example, 22-mer to 30-mer and longer; applying ESC, via current level and density, to discriminate single nucleotide polymorphisms (SNPs); using ESC to improve the overall hybridization of amplified target DNA and RNA sequences on arrays of capture probe oligonucleotides; using ESC to improve the hybridization of any target DNA or RNA sequences on arrays of capture probe oligonucleotides in reverse dot blot formats; using ESC to improve the hybridization of any target DNA or RNA sequences on arrays of capture probe oligonucleotides in sandwich formats; using ESC to improve the hybridization of any DNA or RNA sequence on arrays of nucleic acid sequences in the more classical dot blot format (target sequences on the array, reporter probes added); using ESC to improve the hybridization of target nucleic acid sequences on arrays of nucleic acid probes in homogeneous/heterogeneous hybridization formats; using ESC to improve the hybridization of target RNA sequences on arrays of nucleic acid probes

for gene expression applications; applying independent ESC to individual hybridization events occurring in the same bulk solution and at the same temperature; and using ESC to improve hybridization of un-amplified target DNA sequences to arrays of capture oligonucleotide probes. The nucleotide sequence of the complementary probe will determine the size and sequence of the amplified target DNA. Therefore, the amplified DNA can be custom designed to enhance efficiency in subsequent analysis and/or manipulation. To promote hybridization of complementary nucleic acid in a dilute solution, the sample must be concentrated over the capture sequence. This causes a local increase in the Cot value in the region surrounding the capture, increasing the rate of hybridization by mass action. Under constant current conditions, charge will be transported by all ionic species in the solution and thus the conductance of the solution will determine the proportion of the current carried by the oligonucleotide. Therefore low conductance solutions would be expected to lead to more rapid transport and accumulation of oligonucleotide over the anode. To measure this, fluorescently labeled reporter oligonucleotides were electronically targeted to locations where either complementary or noncomplementary oligonucleotides had previously been attached. The accumulation of fluorescent signal over time in response to the applied current was then assessed for several different buffers (Table 3). Therefore, to accurately measure the effects of conductivity, the initial rate of accumulation was measured. FIG. 20 displays analysis of a representative selection of buffers. The initial increase in fluorescent signal is compared to the inverse of buffer conductivity (i.e. solution resistance). This plot shows a roughly linear relationship between the solution

resistance and the accumulation of signal. The more conductive the solution, the slower the rate of oligonucleotide accumulation.

Using electronic controlled hybridization methods, Sosnowski et al. have found that highly fluorescent sub-micron or nano-scale beads may be used with attached DNA probes for ultra-sensitive assays. Electronic stringency control allows us to utilize these highly fluorescent nanostructures or other multiple labeling scenarios for low copy number (50 to 1000 targets) detection, without any amplification being necessary. In an electric field these particles migrate towards the negatively biased microlocations.

A computer control/data collection system has been designed to provide independent application of electric potentials to any pads in the array and to measure the resulting current flowing in the microlocation-electrolyte system. (Example 11).

Therefore it would have been obvious at the time the invention was to use the electrode method of Sosnowski for the method of Yguerabide. The motivation is that all current micro-scale DNA hybridizations require very high levels of relatively short single-stranded target sequences or PCR amplified DNA, and produce a high level of false positive hybridization signals even under the most stringent conditions (col. 4-5). The disclosed devices of Sosnowski can carry out multi-step and multiplex reactions with complete and precise electronic control. The rate, specificity and sensitivity of multi-step and multiplex reactions are greatly improved at specific microlocations(col. 8-9).

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

6. Claims 423 and 424 are rejected under 35 U.S.C. 102(e) as being anticipated by Wohlstadter et al. (US 6,066,448).

Wohlstadter discloses materials and methods for producing patterned multi-array, multi-specific surfaces which are electronically excited for use in electrochemiluminescence based tests. Materials and methods are provided for the chemical and/or physical control of conducting domains and reagent deposition for use in flat panel displays and multiply specific testing procedures. The invention includes in a broad aspect cassettes for conducting a plurality of electrochemiluminescence assays. The cassettes are formed of supports having thereon a plurality of binding domains able to specifically bind one or more analytes of interest (including nucleic

acid). The binding domains are prepared as patterned, multi-array multi-specific surfaces ("PMAMS") on the support.

The kits comprise components including cassettes suitable for simultaneously measuring a plurality of electrochemiluminescence reactions, support surfaces and upon which a plurality of domains are immobilized assay, media for conduct of the ECL assay conducting chemical reactions. (see claims for example).

Specification

7. The disclosure is objected to because of the following informalities: The continuation data in the specification are incomplete.

If applicant desires priority under 35 U.S.C. § 120 based upon a parent application, specific reference to the parent application must be made in the instant application. It is noted that this appears as the first sentence of the specification following the title. Status of the parent application (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "Patent No." should follow the filing date of the parent application. If a parent application has become abandoned, the expression "abandoned" should follow the filing date of the parent application. Appropriate correction is required.

8. Claims 433-444 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jezia Riley whose telephone number is 703-305-6855. The examiner can normally be reached on 9:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

May 14, 2003

JEZIA RILEY
PRIMARY EXAMINER